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Research Article

Statin Treatment Is Associated With a Neutral Effect on Health-Related Quality of Life Among Community-Dwelling Octogenarian Men: The Helsinki Businessmen Study

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Abstract

Background: Statin treatment is common among 80+ people, but little is known about statin effects on health-related quality of life (HRQoL) in this oldest age group.

Methods: In the Helsinki Businessmen Study (HBS), men born from 1919 to 1934 (original n = 3,490), have been followed-up since the 1960s. In 2015, a questionnaire about lifestyle, diseases, and medications, and including RAND-36/SF-36 HRQoL instrument was mailed to survivors. About 612 men (72.6%) responded, 530 of them reporting their medications (98% community-living). Propensity score analysis was used to compare statin users and nonusers for HRQoL.

Results: We compared 229 current statin users (median age 85 years, interquartile range 84–88 years) with 301 nonusers (86; 84–89 years). Current statin users had had significantly higher serum cholesterol level in midlife (p < .001), but current lifestyle-related characteristics were similar in users and nonusers. Statin users reported more hypertension (61.1%, p < .001), diabetes (23.6%, p <.001), and atherosclerotic cardiovascular disease (ASCVD, 33.6%, p <.001), than nonusers. Statin users reported higher mean scores than nonusers in all eight RAND-36 subscales, but after adjustments for multiplicity and a propensity score we found no significant differences between statin users and nonusers. Stratification for primary (no ASCVD) and secondary (with CVD) prevention supported the main results.

Conclusions: Our study suggests that statin treatment has no significant effect on health-related quality of life among octogenarian, community-dwelling men. The results contradict concerns about statin treatment in the oldest-old, and may caution against deprescribing of statins due to old age alone.

Keywords: Quality of life; Statin treatment; SF-36; Multimorbidities; Drug-related; Frailty.

Octogenarians form an increasing age group in societies, and also use of statin medication is very frequent among them. Although there are no randomized trials on statin treatment performed specifically in 80+ individuals (1,2), observational studies have suggested that statins would have various benefits irrespective of age, frailty, or nutritional status (1,3–11). There are also contradictory results about statin treatment in older individuals (1,12,13), especially in the 80+ group (14). Consequently, the safety of statins and effects on health related quality of life (HRQoL) among older patients and in primary prevention may be of concern (2,15), for example due to well known statin effects on muscle symptoms or risk of diabetes (16). Although these concerns are accentuated in patients with terminal disease (17,18), adverse effects may also impair function and QoL among older people in general. Therefore, statin treatment may be a target for discontinuation and "deprescribing" (17–19) in an older patient because of old age alone. As there are sparse studies

on QoL and statin use in older people living in the community, we investigated this among men with median age of 86 years, 61% of them without a history of atherosclerotic cardiovascular disease (ASCVD).

Materials and Methods

Study Overview

These are secondary analyses of the Helsinki Businessmen Study (HBS), a cohort of men born 1919–1934 (original n = 3,490), who have been followed-up since the 1960s (20,21). Their cardiovascular disease risk factor history (including serum cholesterol values) is known since midlife (mean age 40 years), and their statin use was previously known up to 2010/2011. In 2015, current addresses were retrieved from the Population Information System of Finland for 843 surviving HBS participants, and a questionnaire survey about lifestyle, medications, prevalent physician-diagnosed diseases, and health-related QoL (HRQoL, RAND-36/SF-36 instrument, https://www.rand.org/health/surveys_tools/mos/36-item-short-form.html, 22) was sent to them.

The questionnaire was returned by 612 men (72.6%), with 530 of them presenting a detailed medication list. Of the responders, 520 (98%) were community-living with an age ranging from 80 to 95 years. Primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) were defined as the absence or presence of any of the following reported conditions: coronary artery disease, cerebrovascular disorder (stroke), or peripheral artery disease. Subjective happiness was assessed using a 100-mm scale (0 = most unhappy, 100 = most happy), where the participant was asked to draw X on the point to reflect his feeling of happiness. The men were also asked of their latest cholesterol level, and 292 men reported this.

RAND-36/SF-36 HRQoL instrument includes eight subscales: Role limitations caused by physical health problems (Role physical, RP), Role limitations caused by emotional problems (Role emotional, RE), Vitality (VT), Mental health (MH), Social functioning (SF), Bodily pain (BP), and General health (GH). Scores in subscales range from 0 to 100, with 100 representing the best level of functioning or wellbeing. A difference of 3–5 points in the RAND-36 subscales is considered to be clinically important (22). Use of RAND-36 has been validated in the Finnish population (23).

The prevalence of phenotypic prefrailty and frailty could be assessed in 487 men using the simplified Women's Health Initiative (sWHI) frailty score which has been shown to correlate well with the standard Cardiovascular Health Study (CHS) frailty phenotype (24). Accordingly, we used two items from the RAND-36 Physical function (the capacity to walk one block and scored as severe [two-points]), moderate [1-point], or no limitation [0]), and Vitality subscales (feeling tired most or all of the time [1-point] vs less often [0]), one item for physical activity, and one item for weight loss. A total score of 3 or more defined frailty, a score of 1 or 2 defined pre-frailty, and 0 indicated nonfrailty.

The follow-up has been approved by the ethical committee of the Department of Medicine, Helsinki University Central Hospital. The study is registered as ClinicalTrials.gov identifier: NCT02526082.

Statistical Analysis

Descriptive statistics, Armitage test for trend in proportions, and analysis of covariance (ANCOVA) were used to compare statin users with nonusers. The ANCOVA analyses were adjusted for age, but because statin users had more comorbidity possibly affecting QoL—and may differ also in other respects from nonusers—the presence of health conditions and lifestyle factors were adjusted using a propensity score. The propensity score, defined as the conditional probability of using statins given the individuals covariates (25), was built using the logistic regression model with age, economic situation, living with a spouse, feeling of happiness, alcohol use, BMI, frailty, prevalent diseases (hypertension, diabetes, chronic arrhythmia, pulmonary disease, heart failure, atherosclerotic vascular disease [ASCVD], musculoskeletal disease) as predictors. The propensity score was further divided into quintiles and used as a categorical predictor in the regression models. The 95% confidence intervals were adjusted for multiplicity using Bonferroni's correction procedure. Statistical analyses were performed using NCSS statistical software (Kaysville, UT, www.ncss.com, version 8).

Results

We compared the 229 men currently on statin treatment (median age 85, interquartile range 84–88 years) with the 301 men not using statins (median age 86; interquartile range 84–89 years); their characteristics are presented in Table 1. Among statin nonusers in 2015 we identified 71 men who had discontinued statin for undetermined reasons after 2010/2011, and their characteristics are shown for comparison. Among the men, 299 (61.4%), 165 (33.9%), and 23 (4.7%) men were nonfrail, prefrail, and frail, respectively. There was no significant difference in frailty status between statin users and nonusers (p = .14). Compared to nonusers, current statin users had had significantly higher serum cholesterol level in midlife (mean 6.72 mmol/L, SD 1.1 vs 6.12 mmol/L, SD 1.1; p < .001), but lower reported cholesterol level in 2015 (p < .001). Statin users reported more hypertension (p < .001), diabetes (p < .001), CAD (p < .001), and cerebrovascular disorders (p = .04) than nonusers; of the statin users and nonusers 52.4% and 28.6% had ASCVD, respectively (p < .001). There was no statistically significant difference in the prevalence of cancer, heart failure, chronic arrhythmia, pulmonary disease, or musculoskeletal disease.

Scores of the eight RAND-36 subscales are shown in Table 2. Although the means of all subscales were found to be higher among statin users than all nonusers, we observed no significant differences between the two groups in age-adjusted nor in propensity score-adjusted analyses, also corrected for multiplicity. The scores in scales were generally lower among those who had discontinued statins after 2010/2011 (Table 2).

Finally, we compared RAND-36 subscales between statin users and nonusers separately in primary (no ASCVD) and secondary (history of ASCVD) prevention (Table 3). Men without ASCVD had generally higher mean values of all RAND-36 subscales than men with ASCVD, but otherwise the stratified, adjusted analyses supported the results of the main analysis presented in Table 2.

Discussion

Although octogenarian, community-living statin users had more comorbidity than nonusers of statins, we found no significant differences in HRQoL (RAND-36 subscales) between the two groups. Our results contradict frequent concerns about statin treatment in the oldest-old, one fear being worsened QoL due to adverse effects, for example muscle pain.

In a randomized, unblinded trial of terminal patients expected to live less than 1 year, discontinuation of statin treatment was

Table 1. Characteristics of Statin Users and Nonusers

Variable	Current Nonuser of Statin in 2015, *n* = 301			Current Statin User in 2015, *n* = 229	*p* Between Statin Users and All Nonusers*
	All	Continuous Nonusers, *n* = 230	Discontinued After 2010, *n* = 71		
Age, y, (interquartile range)	86 (84–89)	86 (84–89)	87 (84–90)	85 (84–88)	.014
Cholesterol in midlife, mmol/L	6.12 (0.06)	5.97 (0.08)	6.54 (0.1)	6.72 (0.07)	<.001
Reported cholesterol in 2015, mmol/L, available from 292 men	4.6 (0.1)	4.7 (0.1)	4.3 (0.2)	3.7 (0.1)	<.001
BMI, kg/m^2	24.7 (0.2)	24.7 (0.2)	24.8 (0.4)	25.0 (0.2)	.24
Nonsmokers, *n* (%)	298 (99.0)	233 (96.9)	70 (98.6)	226 (98.7)	.37
Alcohol, g/week	60.8 (4.8)	59.9 (6.0)	77.0 (9.9)	58.0 (5.5)	.81
Living with a spouse, *n* (%)	204 (67.8)	156 (67.7)	46 (65.2)	172 (75.1)	.037
Economic status, *n* (%)					.23
Good	212 (70.4)	168 (73.0)	44 (62.3)	168 (73.3)	
Satisfactory	86 (28.6)	60 (26.1)	26 (36.2)	59 (25.8)	
Bad	3 (1.0)	2 (0.9)	1 (1.4)	2 (0.9)	
Regular physical activity, %)	219 (72.8)	166 (72.2)	53 (74.6)	169 (73.8)	.39
Hours/week (among those with regular activity)	5.0 (0.3)	5.0 (0.4)	5.1 (0.6)	5.0 (0.3)	.99
Regular medication, *n* (%)	251 (83.4)	182 (79.1)	69 (97.2)	229 (100)	<.001
Happiness, mm†	73.1 (0.9)	73.3 (1.0)	72.7 (1.7)	74.2 (1.0)	.39
Stable weight during past 3 months, *n* (%)	234 (77.7)	183 (79.6)	51 (71.8)	179 (78.2)	.40
Phenotypic frailty assessed in 487 men, *n* (%)					.14
Nonfrail	162 (59.3)	145 (63.2)	38 (54.0)	137 (64.0)	
Prefrail	97 (35.5)	71 (30.8)	30 (42.9)	68 (31.8)	
Frail	14 (5.1)	14 (6.0)	2 (3.2)	9 (4.2)	
Reported diseases, *n* (%)					
Diabetes	34 (11.3)	21 (9.1)	13 (18.3)	54 (23.6)	<.001
Hypertension	139 (46.2)	103 (44.8)	36 (50.7)	140 (61.1)	<.001
CAD	46 (15.3)	19 (8.3)	27 (38.0)	77 (33.6)	<.001
Cerebrovascular disorder	31 (10.3	19 (10.1)	12 (16.9)	35 (15.3)	.043
PAD	39 (13.0)	23 (10.0)	16 (22.5)	40 (17.5)	.075
Heart failure	49 (16.3)	31 (13.5)	18 (24.9)	40 (17.5)	.36
Chronic arrhythmia	86 (28.6)	59 (25.7)	27 (38.0)	71 (31.0)	.27
ASCVD‡	87 (28.9)	50 (21.7)	37 (52.1)	121 (52.8)	<.001
Chronic lung disease	33 (11.0)	23 (10.0)	10 (14.1)	23 (10.0)	.37
Cancer	65 (21.6)	50 (21.7)	15 (21.1)	47 (20.5)	.38
Musculoskeletal disease	105 (34.9)	76 (33.0)	29 (40.8)	76 (33.2)	.34

Notes: Continuous variables are mean (*SE*). ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; PAD = Peripheral artery disease; BMI = body mass index.

*Adjusted for age; analysis of covariance (ANCOVA) for continuous variables, Armitage test for trend in proportions. †100 mm line, 0 = most unhappy, 100 = most happy. ‡CAD, cerebrovascular disorder, or PAD.

associated with better QoL (17). However, the interpretation of the results is not unequivocal (26), and in an unblinded trial a reversal of nocebo effect (27) cannot be excluded. In our cohort, statin users reported their HRQoL without knowing the purpose of the present study on statins.

Among the 71 men, who had discontinued statin treatment, HRQoL was generally lower than that of current statin users, but differences were not statistically significant. Reasons of discontinuation were undetermined, and men with worsened QoL due to statin treatment could have been overrepresented among nonusers. Nonadherence has been reported to be especially high among patients older than 75 years (28), but reasons are usually related to lifestyle, not necessarily adverse effects (29). In accordance, discontinuation of statins due to adverse effects has been relatively rare in blinded studies (16), which can adjust for the nocebo effect inflating adverse effects (27) and leading to discontinuation in real life. Despite the possibility for muscle adverse effects, statin treatment did not seem to disturb exercise in the LIFE study (30).

As expected, statin users had more cardiovascular morbidity, but they also tended to have differences in living conditions and lifestyle which could affect QoL. On the other hand, statin treatment has beneficial effects on vascular function (31), anti-inflammatory effects (32), and generally low frequency of real adverse effects (16), all of which would be mechanisms to affect HRQoL, too. Therefore, the analyses were adjusted for using a propensity score analysis in order to tease out potential statin-specific effects on HRQoL. We also performed stratified analyses in primary (without prevalent ASCVD)

Table 2. Health-Related Quality of Life Among Statin Users and Nonusers

	Status of Statin Use in 2015				Mean Difference (95% CI)† Between Current Users and Nonusers of Statins	
	Current Nonusers in 2015			Current Statin Users in 2015, *n* = 229	Age-Adjusted Only‡	Adjusted for Propensity Score§
RAND-36 SUBSCALE*	All Nonusers in 2015, *n* = 301 Mean (*SD*)	Continuous Nonusers, *n* = 230 Mean (*SD*)	Discontinued After 2010, *n* = 71 Mean (*SD*)	Mean (*SD*)		
Physical functioning	63.8 (26.3.)	65.0 (25.5)	60.6 (28.3)	67.9 (24.5)	2.4 (–3.8 to 8.6)	3.8 (–3.1 to 10.8)
Role physical	54.2 (40.1)	54.2 (39.9)	54.2 (40.8)	65.3 (39.0)	9.3 (–0.4 to 19.0)	10.9 (–0.1 to 22.0)
Role emotional	66.8 (38.0)	67.4 (37.3)	62.6 (41.0)	74.3 (35.2)	5.8 (–3.2 to 14.8)	4.4 (–5.9 to 14.7)
Vitality	64.0 (20.4)	65.3 (19.9)	62.0 (21.0)	65.4 (19.5)	1.2 (–3.8 to 6.1)	2.0 (–3.4 to 7.4)
Mental health	80.2 (15.4)	80.5 (15.0)	78.4 (17.1)	82.3 (13.8)	2.1 (–1.5 to 5.7)	1.4 (–2.5 to 5.4)
Social functioning	80.4 (22.6)	81.2 (22.6)	77.9 (23.3)	82.6 (20.7)	1.5 (–3.7 to 6.8)	2.8 (–3.0 to 8.6)
Bodily pain	76.1 (22.3)	77.4 (21.0)	72.0 (25.7)	78.7 (20.3)	2.1 (–3.1 to 7.3)	3.0 (–2.9 to 8.9)
General health	55.3 (17.5)	55.7 (17.4)	53.8 (17.4)	57.8 (17.4)	2.1 (–2.2 to 6.4)	4.1 (–0.6 to 8.9)

Notes: Variables are mean with *SD* in parentheses. CI = confidence interval.

*Score in subscales between 0 (worst) and 100 (best) points. †Bonferroni's correction method used to adjust for multiplicity. ‡Analysis of covariance (ANCOVA). §Propensity score included the following variables: age, economic situation, living with a spouse, feeling of happiness, alcohol use, body mass index, frailty, prevalent diseases (hypertension, diabetes, chronic arrhythmia, pulmonary disease, heart failure, atherosclerotic vascular disease, and musculoskeletal disease).

Table 3. Health-Related Quality of Life in Primary and Secondary Prevention

	Primary Prevention of ASCVD†, *n* = 322			Secondary Prevention of ASCVD†, *n* = 208		
RAND-36 Subscale*	Nonusers of Statins, *n* = 214 Mean (*SD*)	Statin Users, *n* = 108 Mean (*SD*)	Mean Difference (95% CI)‡	Nonusers of Statins, *n* = 87 Mean (*SD*)	Statin Users, *n* = 121 Mean (*SD*)	Mean Difference (95% CI)‡
Physical functioning	68.1 (17.6)	73.2 (23.9)	5.1 (–2.7 to 12.9)	54.7 (27.0)	61.3 (26.4)	6.6 (–4.1 to 17.3)
Role physical	59.5 (38.0)	71.9 (37.4)	12.4 (0.1 to 24.8)	43.8 (42.0)	57.5 (41.8)	13.7 (–2.8 to 30.3)
Role emotional	69.9 (35.1)	77.0 (35.3)	7.1 (–4.4 to 18.7)	61.5 (40.1)	69.6 (39.6)	8.1 (–7.7 to 23.9)
Vitality	67.2 (20.5)	67.9 (19.7)	0.7 (–5.7 to7.1)	56.2 (20.5)	63.1 (19.8)	6.9 (–1.2 to 15.0)
Mental health	81.6 (14.6)	83.0 (14.5)	1.5 (–3.3 to 6.2)	76.8 (15.9)	81.7 (15.4)	4.9 (–1.2 to 10.9)
Social functioning	84.8 (19.0)	87.0 (19.7)	2.2 (–4.1 to 8.5)	70.4 (23.3)	78.2 (23.1)	7.8 (–1.4 to 17.0)
Bodily pain	79.3 (20.5)	81.8 (20.8)	2.5 (–4.1 to 9.2)	68.5 (23.3)	75.5 (22.0)	7.0 (–1.9 to 15.9)
General health	59.4 (17.8)	63.7 (16.6)	4.3 (–1.2 to 9.7)	45.5 (16.8)	51.9 (16.5)	6.4 (–0.2 to 13.1)

Notes: Variables are mean with *SD* in parentheses. CI = confidence interval. ASCVD = atherosclerotic cardiovascular disease.

*Score in subscales between 0 (worst) and 100 (best) points. †Primary and secondary prevention of ASCVD were defined as the absence or presence of any of the following reported conditions: coronary artery disease, stroke, or peripheral artery disease. ‡Age-adjusted, Bonferroni's correction method used to adjust for multiplicity.

and secondary (with ASCVD) prevention which support results in the whole cohort; HRQoL was not significantly different between users and nonusers of statins.

Main limitation of our study is that the cohort of male survivors in a long-term observational study is obviously selected, and over 60% were assessed to be nonfrail. The results nevertheless give information about the associations between statins and HRQoL among community-dwelling octogenarians in real life, and robust or near-robust individuals nevertheless form a substantial proportion of the older population in primary care. A further strength of this homogenous population from the highest social strata is that socioeconomic factors have not been likely to affect the use of statins (which at the time of study were generic in Finland). Healthy user bias—those adhering to statin treatment have also better QoL in the first place—is possible in a cross-sectional study. However, greater comorbidity, especially that of cardiovascular diseases, and similar or higher long-term burden of risk factors in statin users of our cohort (33) do not support it. Moreover, there were no significant differences between users and nonusers in several lifestyle-related factors (BMI, alcohol consumption, smoking, physical activity, economic status), which were nevertheless taken into account in the propensity score analysis. Still, residual confounding is always possible in an observational study, and lack of significant difference does not prove that HRQoL of statin users and nonusers would be equivalent. Although means of several HRQoL subscales were higher among statin users, clinically meaningful difference in RAND-36 subscales is considered to be 3–5 points (22), and lower limits of all confidence intervals were clearly below these. Finally, use of statin was self-reported, but higher cholesterol level in midlife and lower reported cholesterol level in statin users in 2015 suggest that self-report in this cohort is reliable.

In conclusion, our observational study among octogenarian, community-dwelling men showed no significant difference in the health-related quality of life between statin users and nonusers. This neutral finding adds to the cardiovascular benefits of statins and may caution against deprescribing of statins due to old age alone.

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Conflict of Interest

T.E.S. reports various cooperation (educational, research, consultation) with several companies marketing cholesterol-lowering drugs including Amgen, AstraZeneca, Merck, OrionPharma, Pfizer, Servier. Minor stock in OrionPharma (listed company). Other authors declare no conflict of interest related to this paper.

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